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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,005	03/28/2006	Georg Szalkiel	195.66	9324

22497 7590 12/03/2008

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EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
12/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,005	SCZAKIEL ET AL.	
	Examiner	Art Unit	
	CYNTHIA B. WILDER	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-7 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-7 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/25/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/25/2008 has been entered. Claims 5-7 and 14 are pending. Claims 1-4 and 8-13 are pending.

2. This is a continuation of applicant's earlier Application. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Previous Rejections

3. The prior art rejection under 35 USC 102(a) as being anticipated by Rykova et al is withdrawn in view of Applicant's submission of an English language translation of the priority document filed August 18, 2003, thus removing this intervening prior art document. The prior art rejection under 35 USC 103(a) as being unpatentable over Gock et al in view of Hefeneider et al is maintained and discussed below. The prior art rejection under 35 UC 103(a) as being unpatentable over Gocke et al in view of

Hefeneider et al and further in view of Zochbauer-Muller et al is maintained and discussed below.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Once again, claims 5-6 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gocke et al (citation made of record in prior Office action) in view of Hefeneider et al (20020107372, August 8, 2002). With regards to claim 5-6, Gocke et al teach a method for the diagnosis of a disease, wherein the disease is lung cancer (see page 50, lines 25-30), the method comprising the steps of dividing the blood sample of the patient into plasma and cellular fractions, isolating extracellular from the plasma or serum and determining by means of PCR, multiplex amplification,

hybridization or sequencing whether at least two or more nucleic acids are presented among the isolated extracellular nucleic acids, the at least two nucleic acids (APC, p53, and DCC) being diagnostic markers indicative of a disease (see pages 18-20, 23, 26-33, see also page 53, lines 20-30 which teaches detection of multiple different tumor markers). Gocke et al teaches several methods for the isolation of extracellular nucleic acid in plasma or serum, including centrifugation steps (see pages 17-20)

Gocke et al do not teach wherein the isolation of cell-surface bound extracellular nucleic acids comprises the use of PBS/EDTA and a trypsin treatment.

With regards to claim 14, Hefeneider et al provides a general teaching for isolating extracellular nucleic acids which are bonded to the surface of cells of a cellular fraction. Hefeneider et al teach that extracellular DNA are associates with human diseases (0010), including those associated with the lung (0107). Hefeneider et al teach steps of isolating the cell-surface bound extracellular nucleic acid, said method comprising treating the cells with EDTA and PBS, then treating the cells with a trypsin solution (0112 and 0116), Hefeneider et al teach that the trypsin treatment permit cell surface-bound plasmid DNA to be distinguished from internalized plasmid DNA (0120).

Because both Gocke et al and Hefeneider et al teach methods of isolating extracellular DNA for subsequent analysis, such as by PCR, it would have been obvious to one of ordinary skill in the art to substitute one method for the other to achieve the predictable results of isolating extracellular nucleic acid, such as from the surface of cells of a cellular fraction. One of ordinary skill in the art would have been motivated to

target extracellular DNA for the benefit of screening for diseases in an individual as suggested by both Gocke et al and Hefeneider et al.

6. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gocke et al in view of Hefeneider et al as previously applied above and further in view of Zochbauer-Muller (The Oncologist, vol. 7, pages 451-457, 2002), Regarding claim 7, Gocke et al in view of Hefeneider et al teach a method for diagnosing a disease as previously described above, wherein the disease is lung cancer and wherein one of the markers comprise APC.

Gocke et al in view of Hefeneider et al do not teach wherein the diagnostic marker indicative of lung cancer includes RASSF1A.

Zochbauer-Muller et al provides a general teaching of diagnostic markers that are associated with lung cancer. Zochbauer-Muller et al teach the diagnostic marker RASSF1A. Zochbauer-Muller et al teach that RASSF1a methylation may be of prognostic impact in lung cancer patients. Zochbauer-Muller et al teach that patients whose tumors were RASSF1A methylated had a shorter overall survival than patients whose tumors were not RASSF1A methylated (see page 454, col. 2).

Zochbauer-Muller also teaches the marker APC and teaches that low APC methylation is associated a significantly longer survival in lung cancer patients than for patients with high APC methylation status (page 454, col. 2).

Given the multiplex amplification method for detecting diagnostic markers as taught by Gocke et al in view of Hefneider et al, it would have been obvious to one of

ordinary skill in the art at the time of the claimed invention that any combination of gene markers, including APC and RASSF1A, could be predictably detected with a reasonable expectation of success. One of ordinary skill in the art at the time of the claimed invention would have been motivated to target the lung cancer diagnostic markers APC and RASSF1A based on the teaching of Zochbauer-Muller et al that these markers have prognostic impact for lung cancer and thus benefit a patient in regards to treatment strategies.

Response to Arguments

7. Applicant traverses the rejection on the ground that the primary reference of Gocke et al does not disclose applicant's steps of isolating extracellular nucleic acid bonded to the surface of cells of a cellular fraction and determining by PCR, multiplex PCR, hybridization or sequencing whether at least two nucleic acids are present among the isolated extracellular nucleic acids. Applicant states that the Examiner admits that Gocke et al does not teach wherein the isolation of cell-surface based extracellular nucleic acids comprises the use of PBS/EDTA and a trypsin treatment as required in claim 24. Applicant states that Hefeneider et al distinguishes surface binding DNA from internalized plasmid DNA by treating cells with trypsin to remove cell surface proteins. Applicant states that that in contrast, Applicant's method isolates nucleic acids and determining by means of PXCR, multiplex PCR, hybridization or sequencing whether at least two nucleic acids are present and determining that these nucleic acids are indicative of a disease, such as lung cancer. Applicant states that in addition the steps detailed in the claimed 14 are not found in a combination of Gocke et al and Hefneider

et al. Applicant suggests the rejections be withdrawn. With regards to the claim 7, Applicant state that taking the combination of Gocke et al in view of Hefeneider et al and further in view of Zochbauer-Muller as a whole, they identify APC and Rassf1A as diagnostic markers for cancer, but in contrast they do not determine the existence of these markers. Applicant states that the rejection should be withdrawn.

8. All of the arguments have been thoroughly reviewed and considered, but not found persuasive. In response to Applicant's arguments concerning the Gocke et al reference, the Examiner respectfully disagrees. Firstly, it is noted that Gocke et al recognizes the problem in the prior art with looking only at intracellular DNA within circulating cancer cells as a means of only diagnosing cancer as it is limited to the presence of metastatic circulating cancer cells. Gocke teaches that it is of limited use in patients with early cancers and it is not useful in the detection of on-invasive neoplasms or pre-malignant states. Gocke further teaches that the art generally did not recognize that nucleic acid amplification assays can detect tumor associated extracellular mutated DNA, including ocogene DNA in the plasma or serum fraction of blood (see page 4). Gocke et al provides several examples of why the art thought that extracellular nucleic acid did not exist and teaches that it has been found that DNA from tumor cells may be present in the extracellular fluid in the form of proteo-lipid complexes, release of apoptotic bodies from apoptotic tumor cells, or release of free or protein bound DNA from necrotic or lyzed cancer cells (bottom of page 4 bridging top of page 5). Gocke et al teach wherein extracellular DNA has been shown to be present on the cell surface of tumor cells (page 5). Gocke et al's invention sought to provide medically useful

methods of extracting and analyzing all forms of extracellular DNA for the early diagnosis of cancer as Gocke et al asserts that this was not known in the art (see page 5). Contrary to Applicant's arguments, Gocke et al teach wherein at least two nucleic acids are found to be present in the extracellular nucleic acid, said nucleic acids markers indicative of a disease, which is determined by amplification reaction (p53 and bcl-2 (see for example claims 47 and 48).

It is noted that in the claim 1, applicant is reminded that the claim 1 does not require any specific extraction procedures as argued. In the claim 14 however, the Examiner agrees that while Gocke et al teach using EDTA in at least one of the extraction methodologies, Gocke et al does not teach the use of EDTA/PBS and a trypsin treatment as claimed in the claim 14.

7. The Examiner maintains that this teaching is found in the secondary reference of Hefeneider et al as noted in the prior art rejection (see prior office action). In response to applicant's argument that Hefeneider is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Hefeneider et al recognizes the use of EDTA and PBS and subsequent use of trypsin for the isolation of cell surface extracellular nucleic acid. Thus this argument is not found persuasive.

In response to applicant's arguments that the conditions, such as temperature and concentrations are taught in the prior art, it is noted that "[W]here the general

conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller,* 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Routine optimization is not considered inventive and no evidence has been presented that the selection of specific concentrations or incubation temperature was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art. With regards to Applicant's arguments concerning the claim 7, it is noted that while the references of Gocke et al in view of Hefeneider et al do not teach identifying the markers as claimed in the instant invention 7, the Gocke teaches determining the existence of at least two markers in a patient sample that may serve as diagnostic markers for detecting a disease state or condition. The tertiary reference of Zochbauer-Muller teaches the limitation not found the primary reference of Gock et al and provides motivation for why one of ordinary skill in the art would have been motivated to look for the existence APC and RASSF1A for the advantages of determining prognostic treatment strategies for lung cancer as taught by Zochbauer-Muller. Thus this argument is not found persuasive.

Conclusion

8. No claims are allowed. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case.

See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/cbw/

/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637